1. (Amended) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

(a) incubating a nucleic acid sample with one or more first nucleic acid cleaving reagents to produce nucleic acid fragments, wherein the first nucleic acid cleaving reagents are not type IIS restriction enzymes,

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(b) mixing one or more offset adaptors with the nucleic acid sample and covalently coupling the offset adaptors to the nucleic acid fragments,

(c) incubating the nucleic acid sample with one or more second nucleic acid cleaving reagents to produce nucleic acid fragments with sticky ends, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein each offset adaptor has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

(d) mixing one or more adaptor-indexers with the nucleic acid sample and covalently coupling the adaptor-indexers to the nucleic acid fragments, wherein each adaptor-indexer has a different sticky end, wherein each sticky end of the adaptor-indexers is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents,

wherein the nucleic acid fragments to which offset adaptors and adaptor-indexers have been coupled are binary sequence tags.

117. (Amended) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

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(a) incubating a nucleic acid sample with one or more first nucleic acid cleaving reagents to produce nucleic acid fragments, wherein the first nucleic acid cleaving reagents are not type IIS restriction enzymes,

(b) mixing one or more first offset adaptor strands with the nucleic acid sample and covalently coupling the first offset adaptor strands to the nucleic acid fragments, wherein, after coupling, the first offset adaptor strands are fully or partially single-stranded,

(c) treating the nucleic acid sample to result in full or partial complementary sequences hybridized to the first offset adaptor strands,

(d) incubating the nucleic acid sample with one or more second nucleic acid cleaving reagents to produce nucleic acid fragments with sticky ends, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein each first offset adaptor strand has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

(e) mixing one or more adaptor-indexers with the nucleic acid sample and covalently coupling the adaptor-indexers to the nucleic acid fragments, wherein each adaptor-indexer has a different sticky end, wherein each sticky end of the adaptor-indexers is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents,

wherein the nucleic acid fragments to which first offset adaptor strands and adaptor-indexers have been coupled are binary sequence tags.

121. (Amended) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

(a) incubating a nucleic acid sample with one or more first nucleic acid cleaving reagents to produce nucleic acid fragments,

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(b) mixing one or more offset adaptors with the nucleic acid sample and covalently coupling the offset adaptors to the nucleic acid fragments,

(d) incubating the nucleic acid sample with one or more second nucleic acid cleaving reagents to produce nucleic acid fragments with sticky ends, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein each offset adaptor has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

(e) mixing one or more first adaptor-indexer strands with the nucleic acid sample and covalently coupling the first adaptor-indexer strands to the nucleic acid fragments, wherein each first adaptor-indexer strand has a different end sequence, wherein each end sequence of the first adaptor-indexer strands is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents, wherein, after coupling, the first adaptor-indexer strands are fully or partially single-stranded,

wherein the nucleic acid fragments to which offset adaptors and first adaptor-indexer strands have been coupled are binary sequence tags.

126. (Amended) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

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(a) incubating a nucleic acid sample with one or more first nucleic acid cleaving reagents to produce nucleic acid fragments, wherein the first nucleic acid cleaving reagents are not type IIS restriction enzymes,

(b) mixing one or more first offset adaptor strands with the nucleic acid sample and covalently coupling the first offset adaptor strands to the nucleic acid fragments, wherein, after coupling, the first offset adaptor strands are fully or partially single-stranded,

(c) treating the nucleic acid sample to result in full or partial complementary sequences hybridized to the first offset adaptor strands,

(d) incubating the nucleic acid sample with one or more second nucleic acid cleaving reagents to produce nucleic acid fragments with sticky ends, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein each first offset adaptor strand has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

(e) mixing one or more first adaptor-indexer strands with the nucleic acid sample and covalently coupling the first adaptor-indexer strands to the nucleic acid fragments, wherein each first adaptor-indexer strand has a different end sequence, wherein each end sequence of the first adaptor-indexer strands is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents, wherein, after coupling, the first adaptor-indexer strands are fully or partially single-stranded,

wherein the nucleic acid fragments to which first offset adaptor strands and first adaptor-indexer strands have been coupled are binary sequence tags.

Please add the following claims.

127. (New) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

covalently coupling one or more offset adaptors to nucleic acid fragments with sticky ends produced by digestion of a nucleic acid sample with one or more first nucleic acid cleaving reagents, wherein the first nucleic acid cleaving reagents are not type IIS restriction enzymes,

covalently coupling one or more adaptor-indexers to the nucleic acid fragments, wherein the nucleic acid fragments have sticky ends produced by digestion with one or more second nucleic acid cleaving reagents, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein each offset adaptor has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

wherein each adaptor-indexer has a different sticky end, wherein each sticky end of the adaptor-indexers is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents,

wherein the nucleic acid fragments to which offset adaptors and adaptor-indexers have been coupled are binary sequence tags.

128. (New) The method of claim 127 wherein the first nucleic acid cleaving reagents do not cleave at a site offset from their recognition sequence.

129. (New) The method of claim 127 wherein the first nucleic acid cleaving reagents cleave within the recognition sequence.

130. (New) The method of claim 127 wherein at least one of the first nucleic acid cleaving reagents is a Type II restriction enzyme.

131. (New) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

covalently coupling one or more first offset adaptor strands to nucleic acid fragments with sticky ends produced by digestion of a nucleic acid sample with one or more first nucleic acid cleaving reagents, wherein, after coupling, the first offset adaptor strands are fully or partially single-stranded, wherein the first nucleic acid cleaving reagents are not type IIS restriction enzymes,

treating the nucleic acid sample to result in full or partial complementary sequences hybridized to the first offset adaptor strands,

covalently coupling one or more adaptor-indexers to the nucleic acid fragments, wherein the nucleic acid fragments have sticky ends produced by digestion with one or more second nucleic acid cleaving reagents, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein each first offset adaptor strand has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

wherein each adaptor-indexer has a different sticky end, wherein each sticky end of the adaptor-indexers is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents,

wherein the nucleic acid fragments to which first offset adaptor strands and adaptor-indexers have been coupled are binary sequence tags.

132. (New) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

covalently coupling one or more offset adaptors to nucleic acid fragments produced by digestion of a nucleic acid sample with one or more first nucleic acid cleaving reagents,

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covalently coupling one or more first adaptor-indexer strands to the nucleic acid fragments, wherein the nucleic acid fragments have sticky ends produced by digestion with one or more second nucleic acid cleaving reagents, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein each first offset adaptor strand has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

wherein each first adaptor-indexer strand has a different end sequence, wherein each end sequence of the first adaptor-indexer strands is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents, wherein, after coupling, the first adaptor-indexer strands are fully or partially single-stranded,

wherein the nucleic acid fragments to which offset adaptors and first adaptor-indexer strands have been coupled are binary sequence tags.

133. (New) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

covalently coupling one or more first offset adaptor strands to nucleic acid fragments with sticky ends produced by digestion of a nucleic acid sample with one or more first nucleic acid cleaving reagents, wherein, after coupling, the first offset adaptor strands are fully or partially single-stranded, wherein the first nucleic acid cleaving reagents are not type IIS restriction enzymes,

treating the nucleic acid sample to result in full or partial complementary sequences hybridized to the first offset adaptor strands,

covalently coupling one or more first adaptor-indexer strands to the nucleic acid fragments, wherein the nucleic acid fragments have sticky ends produced by digestion with one or more second nucleic acid cleaving reagents, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein each first offset adaptor strand has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

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wherein each first adaptor-indexer strand has a different end sequence, wherein each end sequence of the first adaptor-indexer strands is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents, wherein, after coupling, the first adaptor-indexer strands are fully or partially single-stranded,

wherein the nucleic acid fragments to which first offset adaptor strands and first adaptor-indexer strands have been coupled are binary sequence tags.

134. (New) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

covalently coupling one or more offset adaptors to nucleic acid fragments produced by digestion of a nucleic acid sample with one or more first nucleic acid cleaving reagents,

covalently coupling one or more adaptor-indexers to the nucleic acid fragments, wherein the nucleic acid fragments have sticky ends produced by digestion with one or more second nucleic acid cleaving reagents, wherein the second nucleic acid cleaving reagents cleave at a site offset from their

recognition sequence, wherein each offset adaptor has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

wherein each adaptor-indexer has a different sticky end, wherein each sticky end of the adaptor-indexers is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents,

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wherein the nucleic acid fragments to which offset adaptors and adaptor-indexers have been coupled are binary sequence tags,

mixing a plurality of ligator-detectors with the binary sequence tags and a detector array comprising one or more probes, and covalently coupling the ligator-detectors to the probes,

wherein each ligator-detector comprises sequence matching or complementary to all or part of sequence including, and adjacent to, the sticky end of at least one of the adaptor-indexers, wherein each probe has a different sequence, and

detecting, directly or indirectly, coupling of ligator-detectors to the detector array probes.

135. (New) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

covalently coupling one or more offset adaptors to nucleic acid fragments with sticky ends produced by digestion of a nucleic acid sample with one or more first nucleic acid cleaving reagents, wherein the first nucleic acid cleaving reagents are not type IIS restriction enzymes,

covalently coupling one or more adaptor-indexers to the nucleic acid fragments, wherein the nucleic acid fragments have sticky ends produced by digestion with one or more second nucleic acid cleaving reagents, wherein the second nucleic acid cleaving reagents cleave at a site offset from their

recognition sequence, wherein the second nucleic acid cleaving reagents do not cleave in the recognition sequences of the first nucleic acid cleaving reagents, wherein each offset adaptor has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

wherein each adaptor-indexer has a different sticky end, wherein each sticky end of the adaptor-indexers is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents,

wherein the nucleic acid fragments to which offset adaptors and adaptor-indexers have been coupled are binary sequence tags.

136. (New) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

(a) incubating a nucleic acid sample with one or more first nucleic acid cleaving reagents to produce nucleic acid fragments,

(b) mixing one or more offset adaptors with the nucleic acid sample and covalently coupling the offset adaptors to the nucleic acid fragments,

(c) incubating the nucleic acid sample with one or more second nucleic acid cleaving reagents to produce nucleic acid fragments with sticky ends, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein each offset adaptor has a recognition sequence for at least one of the second nucleic acid cleaving reagents,

(d) mixing one or more adaptor-indexers with the nucleic acid sample and covalently coupling the adaptor-indexers to the nucleic acid fragments, wherein each adaptor-indexer has a

different sticky end, wherein each sticky end of the adaptor-indexers is compatible with one of the possible sticky ends that could be generated by the second nucleic acid cleaving reagents,

wherein the nucleic acid fragments to which offset adaptors and adaptor-indexers have been coupled are binary sequence tags,

(e) mixing one or more ligator-detectors with the binary sequence tags, wherein each ligator-detector comprises sequence matching or complementary to all or part of sequence including, and adjacent to, the sticky end of at least one of the adaptor-indexers,

(f) mixing the nucleic acid sample with a detector array comprising one or more probes and covalently coupling the ligator-detectors to the probes, wherein each probe has a different sequence, and

(g) detecting, directly or indirectly, coupling of ligator-detectors to the detector array probes.

137. (New) A method of producing binary sequence tags from nucleic acid fragments in a nucleic acid sample, the method comprising

(a) incubating a nucleic acid sample with one or more first nucleic acid cleaving reagents to produce nucleic acid fragments,

(b) mixing one or more offset adaptors with the nucleic acid sample and covalently coupling the offset adaptors to the nucleic acid fragments,

(c) incubating the nucleic acid sample with one or more second nucleic acid cleaving reagents to produce nucleic acid fragments with sticky ends, wherein the second nucleic acid cleaving reagents cleave at a site offset from their recognition sequence, wherein the second nucleic acid cleaving reagents do not cleave in the recognition sequences of the first nucleic acid cleaving